Fractal analysis of resting state fMRI signals in adults with ADHD

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Introduction

The fractal concept developed by Mandelbrot (1983) provides a useful tool for examining a variety of naturally occurring phenomena. Fractals are signals that display scale-invariant or self-similar behaviour. They can be found everywhere in nature including fractional Gaussian noise (fGn). Resting state fMRI signals can be modelled as fGn which makes them appropriate for fractal analysis (Maxim, 2005). The Hurst exponent, H, is a measure of fractal processes and has values ranging between 0 and 1. Fractional Gaussian noise with $0<H<0.5$ demonstrates negatively autocorrelated or antipersistent behaviour; fGn with $0.5<H<1$ demonstrates a positively correlated, relatively persistent, predictable, long memory behaviour; and fGn with $H = 0.5$ corresponds to classical Gaussian white noise. Here, memory implies the predictability of a stochastic process where information is gained from the conditional probability of the similar patterns (present and future) that exists in the random process**.** Figure 1 depicts a schematic representation of fGn with H ranging between 0 and 1.

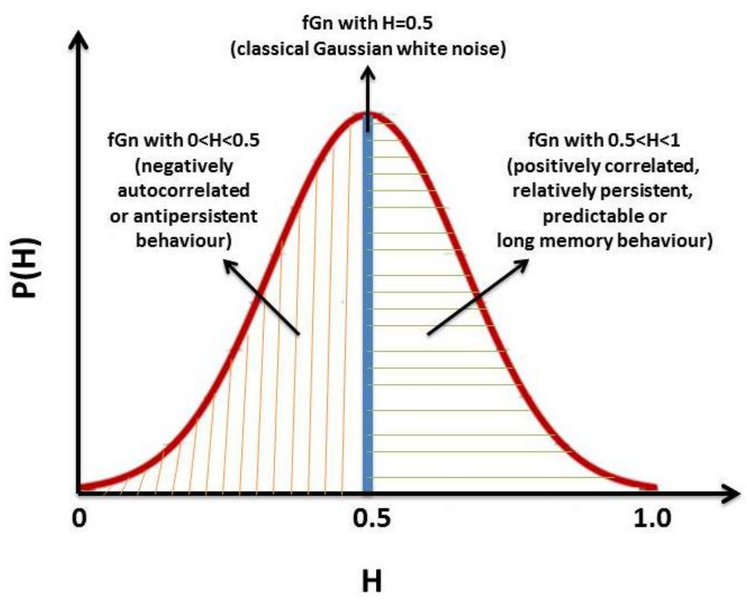

Figure 1: Schematic representation of fractional Gaussian noise (fGn) with Hurst exponent (H) ranging between 0 and 1. P(H) is the probability density function of H.

Several methods for estimating H are available (Fadili and Bullmore, 2002) but the dispersional analysis have been consistently better, requiring smaller datasets and producing less bias. In the present study, we aim to estimate the fractal behaviour of adult ADHD patients when compared to age-matched healthy controls using dispersional analysis. We hypothesize that ADHD patients will demonstrate more predictable (higher H values) fractal behaviour.

Methods

Ten ADHD patients (5 female, mean age (32.60±10.46)) and ten controls (7 female, mean age (30.10±8.49)) were brain imaged by 3T MRI scanner (GE Medical Systems twin-speed Signa HDx) using a 16 channels head coil at resting state. The study was approved by the South West Wales Research Ethics Committee. Exclusion criteria were inability to give informed consent and MRI contraindication. Some of the patients were receiving psychotropic medication for ADHD at the time of scanning. All patients and control participants completed the Conners' Adult ADHD Rating Scales (ADHD scores) (Conners et al., 1999). Functional MR images were acquired with a T_2* weighted gradient echo echo-planar imaging sequence (EPI) in the axial plane with TR of 3000 ms, TE of 35 ms, flip angle of 90º, field of view of 240X240 mm, matrix 64x64, thickness of 4 mm and 31 slices per volume (97 volumes in total after discarding the first three volumes). The fMRI data were pre-processed and characterized generating whole brain H maps (using MATLAB). The statistical analyses were performed with SPSS and SPM8.

Table 1: Statistical analyses of H maps

Statistical test	Talairach coordinate (XYZ)	Brain region (with peak value)	Cluster p value (corrected)	Voxel t value	Cluster extent
Two-sample	-40 -34 8	Left Superior Temporal Gyrus	0.000	8.77	44284
t-test	-22 -24 54	Left Precentral Gyrus		7.78	
(Differences)	-8 -68 0	Left Lingual Gyrus		7.34	
	48 -40 -22	Right Inferior Temporal Gyrus	0.000	7.62	3076
	36 -36 -32	Right Inferior Temporal Gyrus		6.07	
	48 -14 -28	Right Fusiform Gyrus		5.99	
	46 26 -14	Right Inferior Frontal Gyrus	0.005	5.34	656
	28 30 -20	Right Inferior Frontal Gyrus		5.28	
	42 38 -14	Right Middle Frontal Gyrus		4.58	
Multiple	-26 24 -24	Left Inferior Frontal Gyrus	0.001	9.30	941
regression	-20 16 -6	Left Putamen		5.92	
(Correlation)	-34 16 -38	Left Superior Temporal Gyrus		4.69	
	-6 -26 64	Left Medial Frontal Gyrus	0.000	7.85	26645
	-12 -60 -26	Left Culmen		7.38	
	-6 -72 6	Left Cuneus		6.68	

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Results

Figure 2A shows the mean whole brain H differences (p=0.000) between controls (0.7430±0.0491) and patients with ADHD (0.8246±0.0173). When the H maps were tested regionally at a corrected cluster level significance of $p<0.05$, the result of the two-sample t-test (p=0.001) after adjusting for age, shows significant H differences between controls and patients (Figure 2B and Table 1). Here, patients have higher H values than the control group. This implies patients with ADHD portray more predictable fractal behaviour. When the association between the mean whole brain H values and ADHD scores was tested, a significant positive correlation (p=0.000, r=0.738) was detected (Figure 3A). Using an initial threshold of p=0.001, Figure 3B and Table 1 show the regions with significant positive correlations ($p<0.05$) between H and the ADHD scores. This implies the ADHD patients had longer memory fractal behaviour (higher measures of H).

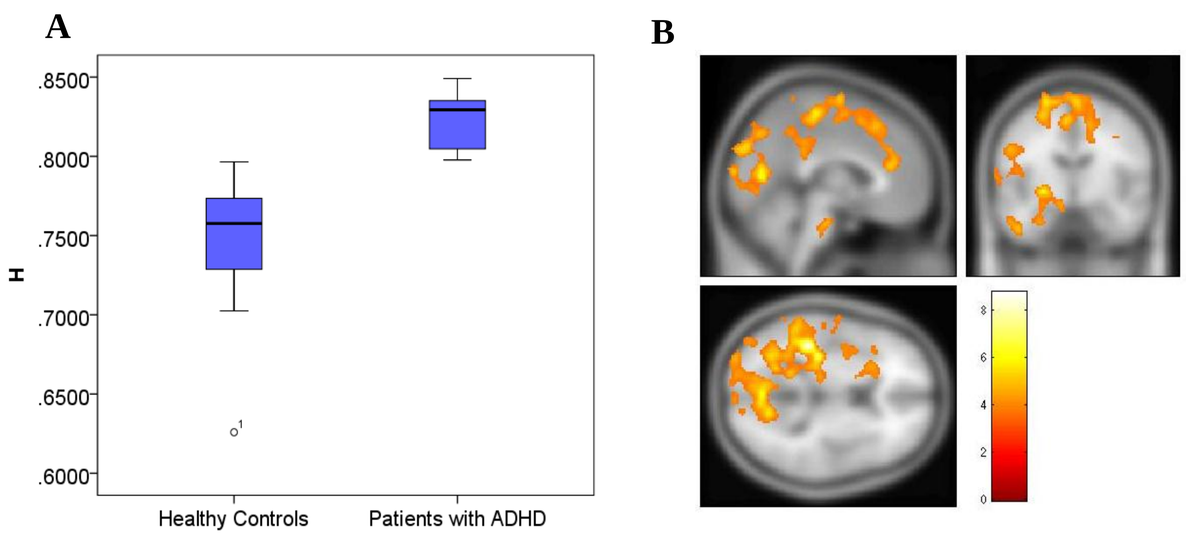

Figure 2: H differences between healthy controls and patients with ADHD. (A) differences in mean whole brain. (B) regional differences in neurological convention. colour bar depicts signal intensity.

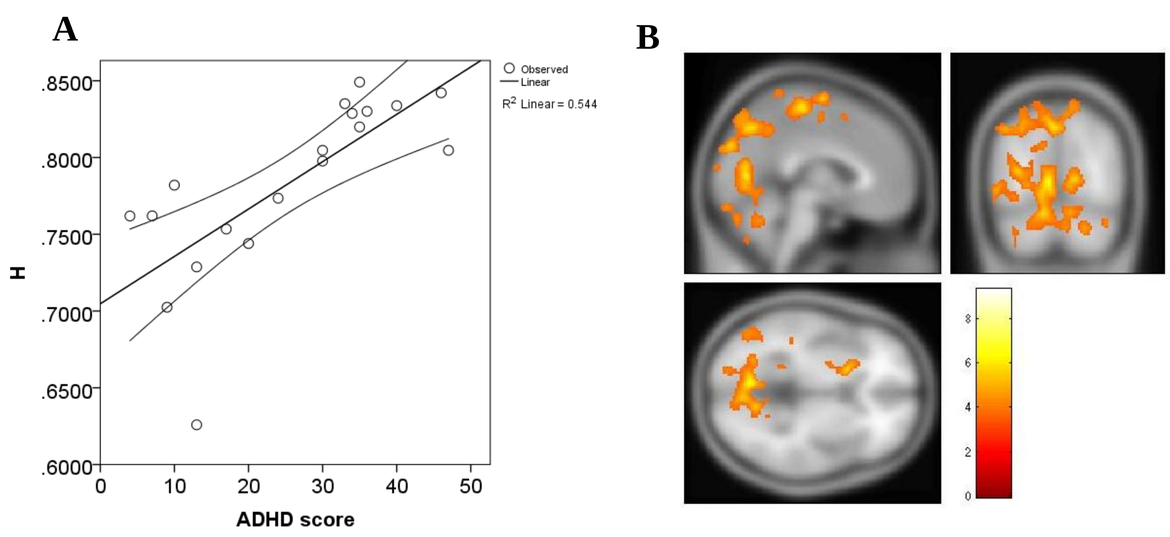

Figure 3: Association of H with ADHD scores. (A) mean whole brain correlations (B) regional correlations in neurological convention. colour bar depicts signal intensity.

Conclusions

Our analysis shows that the ADHD patients demonstrate more positively correlated, relatively persistent, predictable and longer memory fractal behaviour in regards to healthy controls. The discriminated brain regions listed in Table 1 are part of the frontal-striatal-cerebellar circuits and are consistent with the hypothesis of abnormal frontal-striatal-cerebellar circuits in ADHD (Giedd et al. 2001). Our results are similar to previous work in unmedicated ADHD patients (Sun et al. 2012), and are different from the changes observed after dopaminergic medication in ADHD (Wilson et al. 2011). We have shown that the analysis of fractal behaviour may be a useful tool in revealing abnormalities in ADHD brain dynamics.

References

Conners, C.K, Erhardt, D, Sparrow, E.P (1999), 'Conners' Adult ADHD Rating Scales (CAARS)'. North Tonawanda: Multi-Health Systems.

Fadili, J., Bullmore E.T. (2002), 'Wavelet-generalized least squares: a new BLU estimator of linear regression models with 1/*f* errors' *NeuroImage*, vol. 15, pp. 217–32.

Giedd, J.N., Blumenthal, J., Molloy, E., Castellanos, F.X. (2001), 'Brain imaging of attention deficit/hyperactivity disorder' *Ann NYAcad Sci*, vol. 931, pp. 33–49.

Mandelbrot, B. B., (1983), "The fractal geometry of nature". Freeman, San Francisco.

Maxim, V., Sendur, L., Fadili, J., Suckling, J., Gould, R., Howard, R., Bullmore, E., (2005), 'Fractional Gaussian noise, functional MRI and Alzheimer's disease', *Neuroimage*, vol. 25, no. 1, pp. 141-58.

Sun, L., Cao, Q., Long, X., Sui, M., Cao, X., Zhu, C. et al. (2012), 'Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder' *Psychiatry Research: Neuroimaging*, vol. 201, pp. 120–127.

Wilson, T.W., Franzen, J.D., Heinrichs-Graham, E., White, M.L., Knott, N.L., Wetzel, M.W., (2011), 'Broadband neurophysiological abnormalities in the medial prefrontal region of the default-mode network in adults with ADHD', *Hum. Brain Mapp*, doi: 10.1002/hbm.21459